b. a second element comprising a translocation element able to facilitate the transfer of a polypeptide across a vesicular membrane in a pancreatic cell, and

c. a third element comprising a therapeutic element able, when present in the cytoplasm of a pancreatic cell, to inhibit or block enzymatic secretion by said pancreatic cell,

wherein following binding of said first element said composition is transported across a pancreatic cell membrane.

REMARKS

Applicants have amended independent claim 1 to indicate that the composition is transported across a pancreatic cell membrane. This amendment is supported by the specification, e.g., at page 11, lines 11-16.

REJECTION UNDER 35 USC §103(a)

Claims 1-8 and 13-24 stand rejected as allegedly obvious over Foster et al. (WO 9633273) in view of Gaisano et al, *J. Biol. Chem.* 269(25):17062-17066 (1994) and Scheele et al., *Gastroenterology* 92(2):345-353 (1987). Applicants respectfully believe that this rejection is grounded in improper hindsight reconstruction of the invention by picking and choosing elements from various references, wherein the references themselves provide no suggestion, alone or in combination, of the claimed invention when properly considered as a whole.

Applicants firstly incorporate by reference herein the arguments set forth in the Reply filed July 20, 2000 to the rejection of claims 1-8 and 13, 17, and 21 pursuant to 35 USC §103 over the same references, made in the previous Office Action.

The Examiner states that Foster et al. teaches the claimed composition, absent the immunoglobulin hinge region. However, this statement is not accurate with regard to claim 1, which specifically states that the binding element is able to "specifically bind a pancreatic cell surface marker"; Foster does not mention pancreatic cells. Moreover, as claim 1 is

amended herein, Foster does not suggest that the composition described therein may be transported across the pancreatic cell membrane.

While the Examiner correctly points out that Foster indicates that the targeting moiety described therein may bind to a binding site that "undergoes retrograde transport", "retrograde transport" is a term of art referring to a phenomenon particularly seen in neural cells in which an intracellular substance is moved in the direction from nerve terminals to the cell body (and thence often in the dedro-axonal direction to the axon of a neighboring neuron); movement of intraneural substances in the opposite direction is called "orthograde transport". See e.g., Gordon Shepard, *Neurobiology* (3rd. ed. 1994) at 53. A copy of this page is provided for the Examiner's convenience. Additionally, the Foster reference indicates that this is indeed the meaning of the phrase "retrograde transport" meant in that patent application; see Foster page 11, lines 9-13.

Thus, the phrase "retrograde transport" has no meaning with regard to cells other than neural cells, and does not in any way suggest the claimed compositions.

Additionally, with regard to the claims dependent upon Claim 1, Foster does not mention or suggest: a CCK receptor (claim 2), the human CCK A receptor (claim 7), a binding element comprising an amino acid sequence consisting of SEQ ID NO: 6 (claim 8) or SEQ ID NO: 11 (claim 24).

Nevertheless, the Examiner contends that the presently claimed invention is rendered obvious by the combination of Foster et al., Gaisano et al. and Scheele et al.

The Gaisano reference proposes a) that *in vitro* TeTx light chain appears to cleave a subpopulation of a VAMP-2-immunoreactive protein found in a pancreatic zymogen granule membrane fraction, and b) the *in vitro* permeabilization of pancreatic acinar cells with streptolysin O (SLO), followed by treatment of these cells with tetanus toxin light chain, and subsequent measurement of Ca^{++}-stimulated amylase secretion, appears to lessen the appearance of amylase in the media. Gaisano also proposes that zymogen granule membranes contain a protein similar (as determined immunologically) to the VAMP-2 SNARE protein.

As Applicants have pointed out previously, Gaisano acknowledges it was the only group at the time to have made these findings, *id.* at 17064, col.2, and that other groups have obtained results that directly contradict both of these major conclusions, *id.* at 17064, col. 2 and 17065, col. 2; see Stechter et al., *Biochem. J.* 283: 899-904 (1992)) , and Braun et al., *J. Biol. Chem.* 269: 5328-5335 (1994). At the time that the present application was filed, the

person of ordinary skill in the art would have been aware of all three of these references. Thus, Gaisano would, at best, incite the curiosity of such a person as to the veracity of their findings in light of two prior contradictory teachings.

Scheele et al., describe the response of pancreatic acinar cells when exposed to various concentrations of a CCK analog, caerulein. The authors find that at low and normal caerulein concentrations, there is a dose-dependent increase in zymogen granule exocytosis, with amylase appearing normally in pancreatic juice. However, at high concentrations of caerulein, exocytosis is inhibited. The paper indicates that under such conditions secretory enzymes are either released into the lateral intercellular space or are degraded internally within the cell. Scheele at 352.

To the extent that Scheele provides any suggestion concerning a therapeutic for treatment of acute pancreatitis, the paper suggests that over-stimulation of pancreatic cells by caerulein is a cause of the condition. Thus, Scheele states, "supramaximal caerulein or caramylcholine stimulation resulted in the development of acute pancreatitis with pancreatic edema, inflammation and necrosis." *Id.* The paper thus leaves the suggestion that an appropriate therapy for acute pancreatitis would be competitive partial inhibition of caerulein and/or caramylcholine receptor binding, not stimulation of either of these receptors. Again, the cited prior art teaches away from the present invention.

The Examiner alleges that the invention of each of claims 1-8 and 13-24 is obvious in light of a combination of the cited references. It is well established that in order to show obviousness, the prior art must suggest to one of ordinary skill in the art that the invention could be made with a reasonable likelihood of success. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir.1988) (hereinafter *Dow*). As stated by the *Dow* court,

> Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered: for the person of ordinary skill in the art is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.

Dow at 1531, 1532.

Clearly, the combined references fail to suggest the claimed invention. This failure is exacerbated by the ambiguity of the Gaisano reference (which

summarizes papers that clearly appear to teach away from the invention) and the complete silence of the combined primary and secondary references to suggest entire elements of the invention of claim 1 as a whole (e.g., compositions for endocytotic delivery of therapeutic agents to pancreatic cells, the ability of a neurotoxin derivative to be transported across the pancreatic cell membrane).

Thus, the only way that this invention can be said to have been rendered obvious is by using the Applicants' own patent application as a prior art source of motivation, and then attempting to modify the disclosure of Foster et al. to fit the patent claims. Even assuming for the sake of argument that the combination of Foster, Giasano and Sheele make it "obvious to experiment", the *Dow* court has made it clear that "[S]elective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the . . . [invention] other than the knowledge learned from the applicant's disclosure." *Dow* at 1532; *see also In re Rouffet,* 47 USPQ2d 1453, 1457 (Fed Cir. 1998)("[R]ejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be an illogical and inappropriate process by which to determine patentability.")(citations omitted).

Finally, there is no indication in the combination of these references that the CCK receptor could provide a means for targeted uptake of a macromolecular drug similar to that of the presently claimed invention, e.g., a modified neurotoxin within a pancreatic cell. Thus, the combination of the references not only fails to suggest the claimed composition , but none of these references would lead one to believe that the claimed compositions could be internalized and translocated into the cytoplasm of pancreatic cells, or any cells other than neurons. Such a suggestion occurs only in the present specification.

CONCLUSION

For the reasons given above, Applicants again respectfully urge the Examiner to reconsider rejection of the pending claims. If any fee is required in connection with this communication; please use Deposit Account 01-0885 for payment of any fee that may be due.

Respectfully submitted,

Date: 1/22/01

Carlos A. Fisher
Reg. No. 36,510
ALLERGAN, INC.
T2-2E
2525 Dupont Drive
Irvine, CA 92612
Tel: 714-246-4920
Fax: 714-246-4249